REMARKS

This is in response to the USPTO communication dated January 4, 2006 and January 30, 2006. The Examiner has requested that given that there have been further claim amendments, there needs to be a relevant request for reconsideration since there is no indication as to why the instantly pending claims are distinctive over the prior art and otherwise in compliance with 35 USC §112.

In response and in accordance with 37 C.F.R. §1.111, Applicants have canceled claims 245-251 and present new claims 253-254 for further consideration. As will be discussed below, new claims 253 and 254 are supported by the specification and recite specific embodiments. Claim 252 now depends from claim 253. Claims 1-244, 246 248-251 have also been canceled without prejudice. Applicants reserve the right to file subsequent continuation and/or divisional applications on canceled subject matter.

1. Prior Art

As noted above, it is requested that Applicants indicate why the instantly pending claims are distinctive over the prior art. In response, Applicants note that no prior art was applied in the most recent substantive Office Action dated April 1, 2003. However, to be completely responsive, Applicants will point out how the currently pending claims are distinctive over previously cited prior art.

a. DeYoung et al.

DeYoung et al. discloses the expression of ribozymes embedded in a U1 sequence and under the control of a T7 promoter. The ribozyme expressed is used to cleave ANF at various GUC or GUA sites.

The claimed method can be distinguished over DeYoung et al. First, the claimed method involves providing a nucleic acid construct when introduced into a eukaryotic cell produces a **gene product**

comprising a sequence encoding a prokaryotic gene (claim 253) or prokaryotic viral gene (claim 254) and a **sequence non-native to said gene product comprising an intron, where this non-native sequence is removed from the gene product in the eukaryotic cell** and introducing the construct into the eukaryotic cell. In contrast, there is no such disclosure in DeYoung. This is because DeYoung taught the use of recombinantly expressed ribozyme to cleave ANF at various GUC or GUA sites. These GUC and GUA sites are endogenous and native to ANF. Furthermore, the ribozyme was not coexpressed with the ANF. Furthermore, the ribozyme was placed between initiation and termination sequences of U1 snRNA. Neither the U1 or ribozymes act as processing elements, particularly as introns and are certainly not substantially removed during processing. This is actually conceded by the Examiner in the April 2003 Office Action. Specifically, it is stated on page 20

> "DeYoung et al. is no longer considered prior art since they do not teach all the elements of claim 245. The flanking U1 sequences are not removed from the ribozyme sequence upon administration of the plasmid to the cells and expression of the ribozyme".

The same premise would apply to new claims 253 and 254.

b. **Sullenger**

Sullenger et al. teaches a method of expression RNA-based inhibitors of viral replication by localization of an inhibitory RNA such as a ribozyme to a cellular target using a localization signal. "Localization signals" are defined in column 3 as

> Signals which cause the molecule to which they are attached to become localized in certain compartments, and can be readily discovered using standard methodology. These localization siginals may be tethered to the therapeutic agent by any desired procedure, for example, by construction of a

> DNA template which comprises both the localization signal and therapeutic agent RNA as part of the same RNA molecule, or by covalent or ionic bond formation between two moieties.

The currently claimed method can be distinguished from Sullenger et al. Specifically, the constructs used in the method of the present invention comprises a gene product comprising an intron. This intron is substantially removed during processing. The "localization signal" or ribozyme described in Sullenger et al. would certainly not be considered to be an "intron". The expression vectors disclosed by Sullenger do not appear to contain introns.

c. **Hurwitz**

The construct of Hurwitz contains a sequence encoding human serum albumin and at least one intron in the naturally occurring HSA gene. In contrast, the claimed method is directed to a process for selectively expressing a **prolaryotic gene or prokaryotic viral gene**. The construct thus produces a **prokaryotic gene product**. HSA, in contrast, is a eukaryotic gene product.

2. Written Description

In the April 2003 Office Action, it was asserted that an adequate written description of the claimed subject matter was not provided since a representative number of species were not provided.

Applicants had traversed the rejection. Furthermore, Applicants assert that an adequate written description is provided in the currently pending claims. It is supported by the specification on page 81 and page 89, lines 8-13 and Figure 24. For example on page 81, it is stated:

> The present invention provides (1) a universal composition for conditional nucleic acid processing by the introduction of a processing element into a nucleic acid sequence produced from a construct introduced into a cell. Said produced nucleic acid is processed in

> a compatible cell, i.e., a cell capable of processing RNA by removal of a processing element.....
>
> The present invention provides a novel method and constructs for capability for the conditional inactivation of a gene by the use of a non-native, or heterologous, processing element which only permits gene expression in compatible cells. The method utilizes the introduction of a heterologous processing element into the coding region of a desired gene resulting in inactivation of the gene when present in a non-compatible cell. The intron can be inserted at a number sites in most genes.

A eukaryotic cell is an example of a compatible cell since in the method of the present invention, the gene product is **selectively** expressed and the intron is selectively removed in a eukaryotic cell.

On page 89, lines 8-13, it is stated

> The present invention (see Examples) describes the conditional inactivation of a gene (that normally does not contain a processing element (by the precise introduction of an intron between the last two G's of a site that has the post splice junction sequence (C/A)AGG.

Specific examples are provided on pages 86-88 of the specification and include:

a) Conditional inactivation of genes when these genes would be lethal to the host cell or when present in a host cells introduce a danger;

b) Expression of polymerases (e.g., T3, T7 and SP6) in compatible cells.

c) Cloning of incompatible genes together on the same construct, eg., a single construct containing sequences for the production of T7 promoter directed transcript(s) of choice and T7 RNA polymerase

d) Interaction of a non-native gene or its protein products in a cell where the interaction of the introduced genes and/or their gene products can yield useful intracellular processes for gene therapy.

A specific example is set forth in Examples 19 and 20. Example 19 describes the preparation of a eukaryotic vector that expresses T7 RNA polymerase as well as antisense sequences directed by a T7 promoter. A diagrammatic representation is shown in Figure 25. It should be noted that it is stated in Figure 25 "Active T7 RNA polymerase is only made in eucaryotic cells after splicing out of SV40 intron".

3. Enablement

The pending claims were rejected under 35 U.S.C. §112, first paragraph for lack of enablement. It was asserted that the disclosure was enabling for while being enabling for methods of selectively expressing nucleic acid products in a cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing the nucleic acids in a whole organism (*in vivo*).

Applicants respectfully traverse the rejection. However, to advance prosecution, claim 245 has been amended to incorporate the subject matter recited in claim 297. Claims 297 and 298 have been canceled. Claim 290 now recites that the composition is introduced ex vivo into said cell.

Respectfully submitted,

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Dated: 3/30/06

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